Supplementary Online Content

Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. *JAMA*. doi:10.1001/jama.2018.13152

This supplementary material has been provided by the authors to give readers additional information about their work.

eMETHODS

eResults 1. Variant Classification and Reclassification

Variant classification by the testing laboratory was based on ACMG/AMP guidelines as described in **eFigure 1**. Variants were classified at the time of identification based on available functional, statistical, segregation, and literature evidence. All available data were reviewed by a panel of multi-disciplinary experts. Following this review, variants were classified using a 5-tier classification system (**eFigure 1**). A small number of variants did not fit one of these five categories and were classified as Special Interpretation. This indicated to providers that there may be complex or specialized information regarding variant pathogenicity. For example, this classification was given when there was conflicting evidence regarding pathogenicity for variants that would otherwise have been classified as likely Pathogenic (LP) or Pathogenic (P) on ACMG guidelines. In addition, variants given this classification may have interesting features, such as evidence of reduced penetrance or association with the recessive rather than dominant disease state.

BRCA2 c.9699_9702del (p.Cys3233Trpfs*15) is an example of a variant classified as Special Interpretation.[1] This variant results in a frameshift and premature stop codon and is near the 3' end of the gene; however, there are known pathogenic variants downstream of this variant. Based on this information, this variant could be considered pathogenic according to ACMG/AMP guidelines.[2] This variant has also been observed *in trans* (on opposite alleles) with known pathogenic *BRCA2* variants in individuals with features of Fanconi anemia, the expected phenotype for individuals with two pathogenic *BRCA2* variants on opposite alleles. However, it has also been observed *in trans* with known pathogenic *BRCA2* variants in individuals without features of Fanconi anemia. In addition, analysis with the laboratory-developed clinical history weighting algorithm[3,4] shows that the personal and family cancer histories of individuals with this variant are not consistent with those of individuals with known pathogenic *BRCA2* variants. Despite the presence of some evidence that the variant may be benign, the

mechanism of action for this mutation should result in increased cancer risk and the *in trans* presence of the variant does cause Fanconi anemia in some patients. Therefore, this variant does not fit into one of the five classification categories so Special Interpretation is used to alert providers and patients to the uniqueness of this variant.

Reclassification from LP/P to VUS in UTSW Medical Center Subset

Within the subset of patients tested from UTSW Medical Center, three variants were reclassified from P/LP to VUS within this time period. The details of the initial and updated classifications are provided below.

***BRCA1* dup exons 1-22**: At the time that this variant was initially classified as LP, large duplications were generally thought by the medical genetics community to disrupt gene expression and/or function. However, it was later determined that most duplications are oriented in a tandem head-to-tail configuration,[7] which if true for this variant, could result in an intact and functional copy of the gene. With this new evidence, the variant was reclassified to VUS.

***TP53* c.542G>A (p.Arg181His):** This variant was initially classified as LP based on significant published evidence that this variant disrupts apoptosis.[8,9] This variant was reclassified to VUS after re-review of the published functional literature showed that although this variant disrupts one critical tumor suppressor function (apoptosis) of the TP53 protein, other functions may not be significantly impacted leaving question about the pathogenicity.[2-13]

***BRIP1* c.2992_2993del (p.Lys998Glu*3):** This variant was initially classified as P because it results in a frameshift and introduction of a premature stop codon. Based on ACMG/AMP guidelines, such variants are typically pathogenic.[2] However, this variant occurs near the 3' end of the *BRIP1* gene. As noted in the ACMG/AMP guidelines, truncating variants in this region may not actually be pathogenic.[2] Additional review of this end of the *BRIP1* gene left some uncertainty about this area/variant resulting in a reclassification to VUS.

e Results 2. Comparison of Ancestry and Personal Cancer History in Full Cohort versus UTSW Subset

In order to assess demographics information of clinical significance (ancestry, personal cancer history), analyses were performed for exclusive cohorts (full cohort excluding the UTSW subset versus

the UTSW subset). This resulted in slightly different results for the full cohort (excluding the UTSW cohort) compared to the full cohort (including the UTSW cohort) reported in Table 1.

All comparisons were significant. For all hereditary cancer testing, the differences between the full testing cohort versus the UTSW cohort were significant ($p<0.001$): European, 51.9% versus 43.5%; Latin American or Caribbean, 6.5% versus 21.0%; African, 5.6% versus 15.1%; Asian, 2.6% versus 2.8%; Native American, 1.3% versus 0.1%; Near or Middle Eastern, 0.8% versus 1.6%; Multiple, 9.1% versus 9.5%; None Specified, 22.4% versus 6.3%. For single-syndrome testing, the differences between the full testing cohort versus the UTSW subset were significant ($p<0.001$): European, 52.9% versus 48.0%; Latin American or Caribbean, 6.3% versus 17.7%; African, 5.5% versus 14.3%; Asian, 2.7% versus 2.9%; Native American, 1.2% versus 0.2%; Near or Middle Eastern, 0.8% versus 1.6%; Multiple, 8.7% versus 8.4%; None Specified, 22.0% versus 7.0%. For panel testing, the differences between the full testing cohort versus the UTSW cohort were significant ($p<0.001$): European, 48.3% versus 34.6%; Latin American or Caribbean, 7.4% versus 27.5%; African, 6.1% versus 16.8%; Asian, 2.4% versus 2.8%; Native American, 1.3% versus 0.1%; Near or Middle Eastern, 0.7% versus 1.5%; Multiple, 10.5% versus 11.8%; None Specified, 23.2% versus 4.8%.

Similar to ancestry, the statistical significance of personal cancer history differences was assessed by evaluating the data for the exclusive full testing cohort versus the UTSW subset using Fisher's exact test, as above. For all hereditary cancer testing, the differences between the full testing cohort versus the UTSW cohort were significant ($p<0.001$): Affected, 56.6% versus 71.5%; Unaffected, 35.3% versus 25.6%; Polyps Only, 1.3% versus 1.5%; Not Specified, 6.8% versus 1.4%. For single-syndrome testing, the differences between the full testing cohort versus the UTSW cohort were significant ($p<0.001$): Affected, 60.6% versus 77.7%; Unaffected, 29.6% versus 18.5%; Polyps Only, 1.3% versus 1.7%; Not Specified, 8.5% versus 2.1%. For panel testing, the differences between the full testing

cohort versus the UTSW cohort were significant ($p<0.001$): Affected, 42.7% versus 59.3%; Unaffected, 56.0% versus 39.6%; Polyps Only, 1.2% versus 0.9%; Not Specified, 0.1% versus 0.1%.

eTable 1. Genes included in genetic testing from the single commercial laboratory included in this study

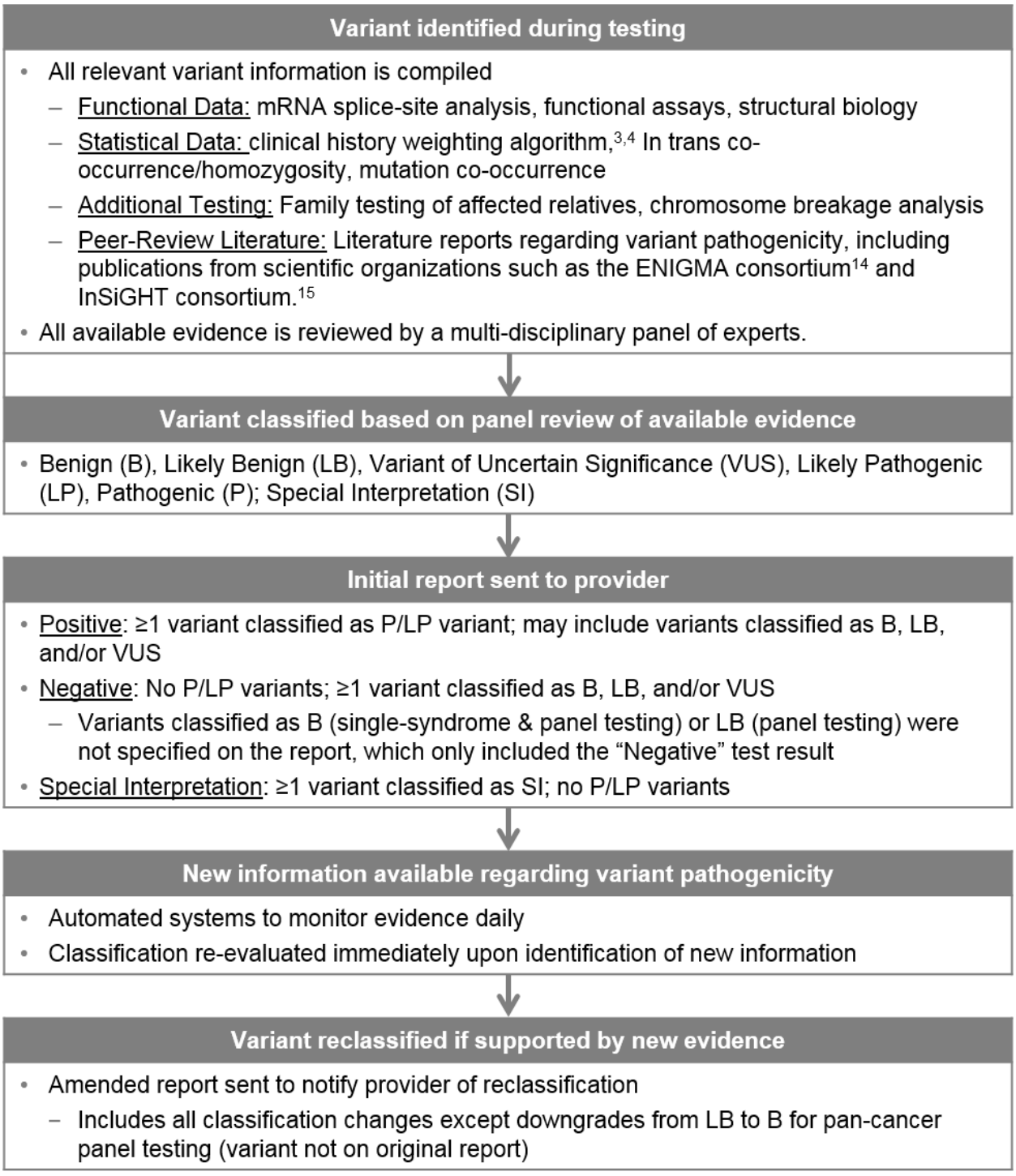
Test Type	Genes Included (NCBI Accession)
Hereditary Breast and Ovarian Cancer syndrome (HBOC) Testing	*BRCA1* (672), *BRCA2* (675)
Lynch Syndrome Testing	*MLH1* (4292), *MSH2* (4436), *MSH6* (2956), *PMS2* (5395), *EPCAM* (4072)
Familial Adenomatous Polyposis (FAP) Testing	*APC* (324)
MUTYH-Associated Polyposis (MAP) Testing	*MUTYH* (4595)
Hereditary Pancreatic Cancer Testing	*PALB2* (79728), *BRCA2* (675)
Hereditary Melanoma Testing	*CDKN2A* (1029)
Pan-Cancer Panel Testing*	*APC* (324) , *ATM* (472), *BARD1* (580), *BMPR1A* (657), *BRCA1* (672), *BRCA2* (675), *BRIP1* (83990), *CDH1* (999), *CDK4* (1019), *CDKN2A* (p16INK4a and p14ARF) (1029), *CHEK2* (11200), *EPCAM* (4072), *GREM1*** (26585), *MLH1* (4292), *MSH2* (4436), *MSH6* (2956), *MUTYH* (4595), *NBN* (4683), *PALB2* (79728), *PMS2* (5395), *POLD1*** (5424), *POLE*** (5426), *PTEN* (5728), *RAD51C* (5889), *RAD51D* (5892), *STK11* (6794), *SMAD4* (4089), *TP53* (7157)

*Initially offered in September 2013

**Added to multi-gene panel test in July 2016.

Abbreviation: **NCBI,** National Center for Biotechnology Information gene data base

eFigure 1. Summary of the testing laboratory process for variant classification and reporting.



eTable 2. Distribution of variants initially classified as variant of uncertain significance by gene for the full clinical testing cohort.

Gene	Initially Reported VUSs			Reclassified VUSs			Amended Reports*	
	N	**%**		**N**	**%**		**N**	**%**
APC	13,302	7.22		537	1.15		680	1.19
ATM	24,282	13.17		8,768	18.70		10,085	17.67
BARD1	6,539	3.55		1,206	2.57		1,334	2.34
BMPR1A	2,404	1.30		226	0.48		280	0.49
BRCA1	12,080	6.55		5,491	11.71		7,044	12.34
BRCA2	28,224	15.31		12,478	26.61		16,090	28.19
BRIP1	7,973	4.33		1,478	3.15		1,731	3.03
CDH1	6,150	3.34		944	2.01		1,103	1.93
CDK4	1,346	0.73		54	0.12		57	0.10
CDKN2A (p14ARF)	1,427	0.77		29	0.06		33	0.06
CDKN2A (p16INK4a)	4,606	2.50		841	1.79		1,013	1.77
CHEK2	9,332	5.06		1,799	3.84		1,939	3.40
EPCAM	45	0.02		0	0		0	0.0
GREM1	0	0		0	0		0	0
MLH1	3,918	2.13		1,306	2.79		1,665	2.92
MSH2	5,688	3.09		1,408	3.00		1,809	3.17
MSH6	8,905	4.83		1,797	3.83		2,197	3.85
MYH	6,429	3.49		290	0.62		320	0.56
NBN	8,987	4.88		865	1.84		1,120	1.96
PALB2	6,136	3.33		2,554	5.45		2,875	5.04
PMS2	8,657	4.70		1,257	2.68		1,411	2.47
POLD1	118	0.06		0	0.0		0	0.0
POLE	219	0.12		0	0.0		0	0.0
PTEN	1,061	0.58		143	0.30		187	0.33
RAD51C	4,454	2.42		778	1.66		873	1.53
RAD51D	4,353	2.36		921	1.96		1,089	1.91
SMAD4	1,922	1.04		237	0.51		334	0.59
STK11	2,797	1.52		482	1.03		593	1.04
TP53	2,973	1.61		1,001	2.13		1,214	2.13
TOTAL	184,327	100		46,890	100		57,076	100

Abbreviations: VUS, variant of uncertain significance

*Amended reports may contain multiple variants. The values in this column include any amended report that included a variant in the listed gene.

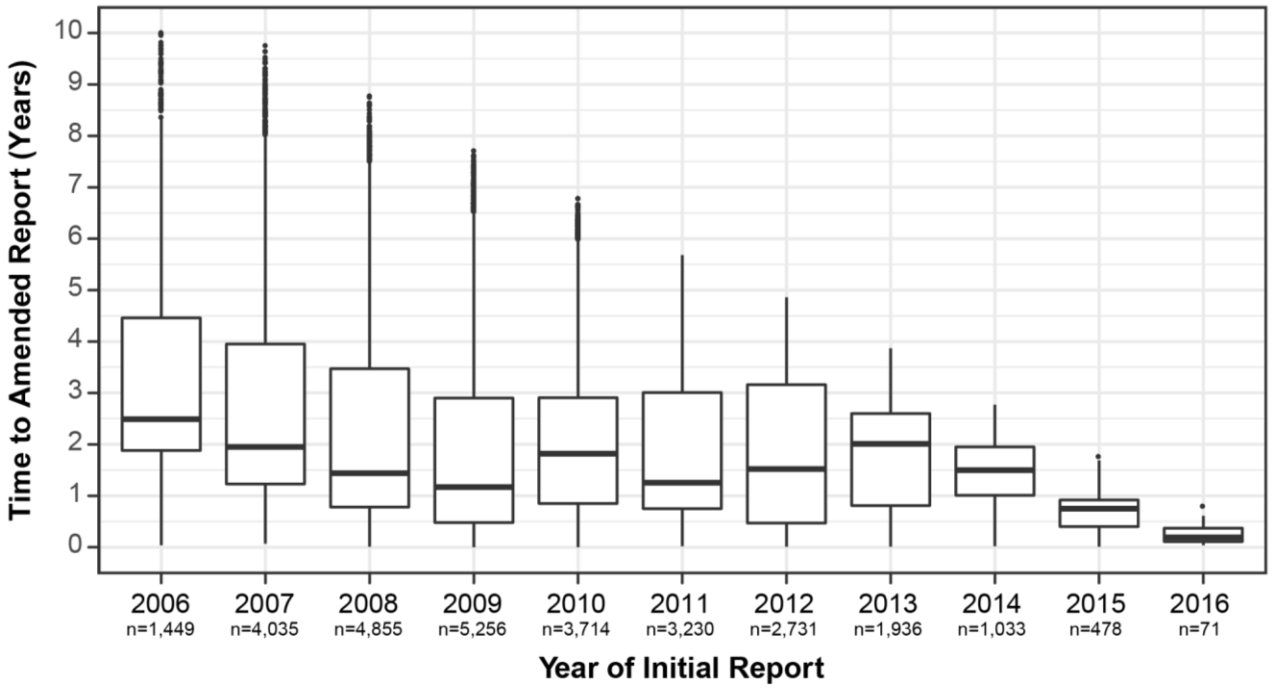
eTable 3. Distribution of variants initially classified as variant of uncertain significance by gene for the subset of patients tested through the University of Texas Southwestern Medical Center.

Gene	Initially Reported VUSs			Reclassified VUSs			Amended Reports*	
	N	**%**		**N**	**%**		**N**	**%**
APC	155	7.97		13	2.38		13	2.29
ATM	311	15.99		136	24.86		136	23.99
BARD1	73	3.75		21	3.84		21	3.70
BMPR1A	18	0.93		3	0.55		3	0.53
BRCA1	72	3.70		34	6.22		39	6.88
BRCA2	179	9.20		65	11.88		82	14.46
BRIP1	88	4.52		20	3.66		20	3.53
CDH1	62	3.19		15	2.74		15	2.65
CDK4	12	0.62		0	0.0		0	0.0
CDKN2A (p14ARF)	16	0.82		0	0.0		0	0.0
CDKN2A (p16INK4A)	112	5.76		23	4.20		23	4.06
CHEK2	99	5.09		11	2.01		11	1.94
EPCAM	1	0.05		0	0.0		0	0.0
GREM1	0	0		0	0		0	0
MLH1	36	1.85		6	1.10		6	1.06
MSH2	55	2.83		12	2.19		12	2.12
MSH6	85	4.37		15	2.74		13	2.29
MYH	73	3.75		2	0.37		2	0.35
NBN	121	6.22		42	7.68		42	7.41
PALB2	82	4.22		49	8.96		49	8.64
PMS2	74	3.80		14	2.56		14	2.47
POLD1	2	0.10		0	0.0		0	0.0
POLE	5	0.26		0	0.0		0	0.0
PTEN	18	0.93		10	1.83		10	1.76
RAD51C	30	1.54		6	1.10		6	1.06
RAD51D	63	3.24		17	3.11		17	3.00
SMAD4	15	0.77		3	0.55		3	0.53
STK11	29	1.49		9	1.65		9	1.59
TP53	59	3.03		21	3.84		21	3.70
TOTAL	1945	100		547	100		567	100

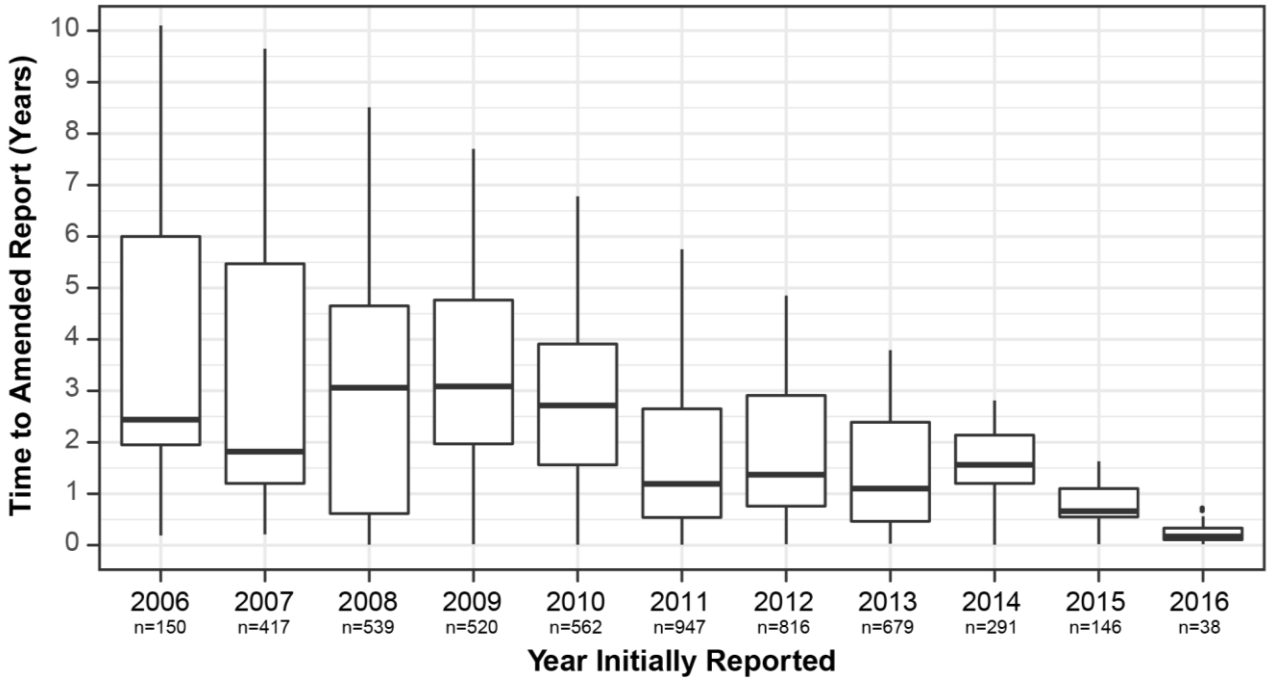
Abbreviations: VUS, variant of uncertain significance

*Amended reports may contain multiple variants. The values in this column include any amended report that included a variant in the listed gene.

eFigure 2. Year-specific Time to Reclassification for BRCA1/2 variants.
For amended reports sent due to the reclassification of variants in *BRCA1* and/or *BRCA2*, the time to amended report is shown according to the year of the initial report. Pan-cancer panel testing was introduced in 2013. Prior to 2013, all amended reports were for single-syndrome testing. The median time for each year is indicated by the thick horizontal line and the interquartile range is indicated by the box. The error bars represent 1.5 times the interquartile range. Data points beyond error bars represent outlying points.



eFigure 3. Year-specific Time to Reclassification for MMR gene variants.
For amended reports sent due to the reclassification of variants in genes associated with Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), the time to amended report is shown according to the year of the initial report. Pan-cancer panel testing was introduced in 2013. Prior to 2013, all amended reports were for single-syndrome testing. The median time for each year is indicated by the thick horizontal line and the interquartile range is indicated by the box. The error bars represent 1.5 times the interquartile range. Data points beyond error bars represent outlying points.



eTable 4. Initial classification and reclassification details for variants of uncertain significance that were reclassified as part of single-syndrome testing for full cohort.

	Upgrades					Downgrades					Reclassification to or from Special Interpretation	Total
Original Classification	**B**	**B/LB**	**VUS**	**VUS**	**LP**	**P**	**P**	**LP**	**VUS**	**LB**		
Reclassification	**LB**	**VUS**	**LP**	**P**	**P**	**LP**	**VUS**	**VUS**	**B/LB**	**B**		
APC	0	2	21	7	0	0	0	7	342	200	29	608
BRCA1	0	8	346	55	300	0	2	41	4908	3771	210	9641
BRCA2	1	1	395	58	562	0	5	125	11592	7119	200	20058
CDKN2A (p16INK4a)	0	0	6	0	1	0	0	0	7	30	0	44
MLH1	0	12	152	18	187	0	0	10	552	429	47	1407
MSH2	0	5	98	19	137	0	0	6	752	435	16	1468
MSH6	0	0	52	5	39	0	1	0	1041	732	0	1870
MUTYH	0	0	2	2	3	0	0	0	112	33	0	152
PALB2	0	0		0	0	0	0	0	16	11	0	27
PMS2	0	0	0	7	0	0	0	0	327	111	0	445
TOTAL	1	28	1072	171	1229	0	8	189	19649	12871	502	35720

Abbreviations: B, Benign; LB, Likely Benign; P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance

eTable 5. Initial classification and reclassification details for variants of uncertain significance that were reclassified as part of pan-cancer panel testing for full cohort.

	Upgrades				Downgrades				Reclassification to or from Special Interpretation	Total
Original Classification	**B/LB**	**VUS**	**VUS**	**LP**	**P**	**P**	**LP**	**VUS**		
Reclassification	**VUS**	**LP**	**P**	**P**	**LP**	**VUS**	**VUS**	**B/LB**		
APC	0	1	0	0	0	0	0	166	4	171
ATM	3	49	0	0	0	0	0	8726	0	8778
BARD1	1	0	0	0	0	0	2	1206	0	1209
BMPR1A	0	0	0	0	0	0	0	227	0	227
BRCA1	0	12	7	12	0	1	0	204	6	242
BRCA2	0	3	0	13	0	0	0	510	2	528
BRIP1	0	1	0	0	0	6	0	1477	0	1484
CDH1	0	2	0	0	0	0	0	942	0	944
CDK4	0	0	0	0	0	0	0	54	0	54
CDKN2A (p14ARF)	0	0	0	0	0	1	0	29	0	30
CDKN2A (p16INK4a)	0	0	0	0	0	0	0	828	0	828
CHEK2	0	58	0	0	0	0	0	1742	0	1800
MLH1	3	6	0	15	0	0	0	565	5	594
MSH2	0	12	0	10	0	0	0	540	10	572
MSH6	2	11	0	20	0	0	0	695	0	728
MUTYH	2	0	0	0	0	0	0	174	0	176
NBN	0	0	0	0	0	4	2	866	116	988
PALB2	0	0	0	7	0	0	0	2540	0	2547
PMS2	0	0	2	0	0	0	0	923	0	925
PTEN	0	4	0	0	0	0	0	139	0	143
RAD51C	0	6	0	0	0	1	0	772	0	779
RAD51D	0	0	0	0	0	9	0	922	0	931
SMAD4	0	0	0	0	1	0	0	237	0	238
STK11	0	0	0	0	0	0	0	482	0	482
TP53	0	0	2	0	0	1	11	990	9	1013
TOTAL	11	165	11	77	1	23	15	25956	152	26411

Abbreviations: B, Benign; LB, Likely Benign; P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance

eTable 6. Classification and reclassification details for variants of uncertain significance that were reclassified as part of single-syndrome testing for the University of Texas Southwestern Medical Center cohort.

	Upgrades					Downgrades					Reclassification to or from Special Interpretation	Total
Original Classification	**B**	**B/LB**	**VUS**	**VUS**	**LP**	**P**	**P**	**LP**	**VUS**	**LB**		
Reclassification	**LB**	**VUS**	**LP**	**P**	**P**	**LP**	**VUS**	**VUS**	**B/LB**	**B**		
APC	0	0	0	0	0	0	0	0	11	4	1	16
BRCA1	0	0	1	2	1	0	0	1	26	30	0	61
BRCA2	0	0	2	1	4	0	0	0	55	35	1	98
CDKN2A (p16INK4a)	0	0	0	0	0	0	0	0	0	0	0	0
MLH1	0	0	1	0	2	0	0	0	1	0	0	4
MSH2	0	0	0	0	0	0	0	0	3	0	1	4
MSH6	0	0	1	0	0	0	0	0	5	7	0	13
MUTYH	0	0	0	0	0	0	0	0	1	1	0	2
PALB2	0	0	0	0	0	0	0	0	0	0	0	0
PMS2	0	0	0	0	0	0	0	0	4	0	0	4
TOTAL	0	0	5	3	7	0	0	1	106	77	3	202

Abbreviations: B, Benign; LB, Likely Benign; P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance

eTable 7. Classification and reclassification details for VUS that were reclassified as part of pan-cancer panel testing for the University of Texas Southwestern Medical Center cohort.

	Upgrades				Downgrades				Reclassification to or from Special Interpretation	Total
Original Classification	**B/LB**	**VUS**	**VUS**	**LP**	**P**	**P**	**LP**	**VUS**		
Reclassification	**VUS**	**LP**	**P**	**P**	**LP**	**VUS**	**VUS**	**B/LB**		
APC	0	0	0	0	0	0	0	2	0	2
ATM	1	0	0	0	0	0	0	136	0	137
BARD1	0	0	0	0	0	0	0	21	0	21
BMPR1A	0	0	0	0	0	0	0	3	0	3
BRCA1	0	0	1	0	0	0	0	3	0	4
BRCA2	0	0	0	0	0	0	0	7	0	7
BRIP1	0	0	0	0	0	1	0	20	0	21
CDH1	0	1	0	0	0	0	0	14	0	15
CDK4	0	0	0	0	0	0	0	0	0	0
CDKN2A (p14ARF)	0	0	0	0	0	0	0	0	0	0
CDKN2A (p16INK4a)	0	0	0	0	0	0	0	23	0	23
CHEK2	0	1	0	0	0	0	0	10	0	11
MLH1	0	0	0	0	0	0	0	4	1	5
MSH2	0	0	0	0	0	0	0	9	1	10
MSH6	0	0	0	0	0	0	0	10	0	10
MUTYH	0	0	0	0	0	0	0	1	0	1
NBN	0	0	0	0	0	0	0	42	1	43
PALB2	0	0	0	0	0	0	0	49	0	49
PMS2	0	0	0	0	0	0	0	10	0	10
PTEN	0	0	0	0	0	0	0	10	0	10
RAD51C	0	0	0	0	0	0	0	6	0	6
RAD51D	0	0	0	0	0	0	0	17	0	17
SMAD4	0	0	0	0	0	0	0	3	0	3
STK11	0	0	0	0	0	0	0	9	0	9
TP53	0	0	0	0	0	0	1	21	3	25
TOTAL	1	2	1	0	0	1	1	430	6	442

Abbreviations: B, Benign; LB, Likely Benign; P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance

eTable 8. Details of variant reclassification and clinical history for cases from the University of Texas Southwestern Medical Center where VUSs were reclassified to or from pathogenic or likely pathogenic.

Gene	Variant	Initial	New	Time to Amended Report, mos	Reason for Reclassification	Personal Cancer History*	Family Cancer History*	Surgical History*	Follow-Up
BRCA1	Dup exons 1-22	LP	VUS	65	Re-evaluation with updated knowledge and peer reviewed literature	Unilateral BC at 58	BC, LC, skin, throat, leukemia	BM, TAH-BSO**	None
TP53	c.542G>A, (p.Arg181His)	LP	VUS	8	Re-evaluation of peer reviewed literature	Unilateral BC at 39	None	BM	Managed as LFS with possible risks still conferred
BRIP1	c.2992_2993del (p.Lys998Glu*3)	P	VUS	9	Re-evaluation of evidence for truncating variants at the 3' end of *BRIP1*	None	BC, CRC, PC, liver, melanoma	None	GI screening based on APC AJ variant, c.3920T>A (p.Ile1307Lys) family history
BRCA1	c.5453A>G (p.Asp1818Gly)	VUS	P	26	Clinical history weighting algorithm, segregation	None	BC	BSO**	Declined high risk screening; diagnosed with breast cancer
BRCA1	c.5165C>T (p.Ser1722Phe)	VUS	P	22	Clinical history weighting algorithm, segregation, published functional studies	Unilateral BC at 39	EC	Lumpectomy	Relative diagnosed with OC prior to reclassification; Proband had BSO after reclassification
BRCA1	c.4484G>A (p.Arg1495Lys)	VUS	P	6	Internal mRNA splice site analysis, clinical history weighting algorithm	Unilateral BC at 59, OC at 61	None	Lumpectomy, TAH-BSO**	None

BRCA1	c.5365G>A (p.Ala1789Thr)	VUS	LP	13	Published functional studies, structural biology analysis	Unilateral BC at 42	None	UM	None
BRCA2	c.316+5G>A	VUS	P	4	Published functional studies, clinical history weighting algorithm	None	Breast	None	Prophylactic bilateral mastectomies after reclassification
BRCA2	c.8377G>A, (p.Gly2793Arg)	VUS	LP	28	Structural biology analysis, segregation	Unilateral BC at 39	PC, BC, CRC, abdominal	UM	None
BRCA2	c.8168A>G (p.Asp2723Gly)	VUS	LP	10	Published functional studies, segregation	Unilateral BC at 28	EC	BM	TAH-BSO after reclassification
CDH1	c.1137+1G>A	VUS	LP	15	Peer reviewed literature (functional and clinical evidence)	None	OC	None	None
CHEK2	c.846+4_846+7del	VUS	LP	3	Internal mRNA splice site analysis	Unilateral BC at 54	BC, LC, PC, thyroid, GB	UM	None
MLH1	c.83C>T (p.Pro28Leu)	VUS	LP	4	Segregation, structural biology analysis, published functional studies	CRC at 43	Leukemia, melanoma, PC	Partial colon resection, TAH-BSO**	None
MSH6	c.4001G>A (p.Arg1334Gln)	VUS	LP	86	Internal mRNA splice site analysis	CRC at 46	BC, CRC	Partial colon resection	Managed as Lynch syndrome based on Amsterdam II criteria prior to reclassification

Abbreviations: AJ, Ashkenazi Jewish; BC, Breast Cancer; BM, Bilateral mastectomy; BSO, bilateral salpingo-oophorectomy; CRC, Colorectal Cancer; EC, Endometrial cancer; FHx, Family cancer history; GB, glioblastoma; LC; Lung cancer; LFS, Li Fraumeni syndrome; OC, Ovarian cancer; PHx, Personal cancer history; PC, Prostate cancer; TAH, total abdominal hysterectomy; P/LP, Pathogenic/Likely Pathogenic; UM, Unilateral mastectomy; VUS, variant of uncertain significance. *At time of initial test report. **Surgical intervention performed prior to receipt of the initial genetic test report.

eReferences

1. Rosenthal ET, Bowles KR, Pruss D, et al. Exceptions to the rule: case studies in the prediction of pathogenicity for genetic variants in hereditary cancer genes. *Clin Genet.* 2015;88(6):533-541.
2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405-424.
3. Morris B, Hughes E, Rosenthal E, Gutin A, Bowles KR. Classification of genetic variants in genes associated with Lynch syndrome using a clinical history weighting algorithm. *BMC Genetics.* 2016;17(1):99.
4. Pruss D, Morris B, Hughes E, et al. Development and validation of a new algorithm for the reclassification of genetic variants identified in the BRCA1 and BRCA2 genes. *Breast Cancer Res Treat.* 2014;147(1):119-132.
5. R Development Core Team. R: A Language and Environment for Statistical Computing. 2014; http://www.R-project.org.
6. Wickham H. *ggplot2: Elegant Graphics for Data Analysis.* Houston, Texas: RStudio; 2009.
7. Newman S, Hermetz KE, Weckselblatt B, et al. Next-Generation Sequencing of Duplication CNVs Reveals that Most Are Tandem and Some Create Fusion Genes at Breakpoints. *Am J Hum Genet.* 2015;5(96):208-220.
8. Wang XW, Vermeulen W, Coursen JD, et al. The XPB and XPD DNA helicases are components of the p53-mediated apoptosis pathway. *Genes & Development*. 1996;10:1219-1232.
9. Schlereth K, Beinoraviciute-Kellner R, Zietlinger MK, et al. DNA Binding Cooperativity of p53 Modulates the Decision between Cell-Cycle Arrest and Apoptosis. *Molecular Cell.* 2010;38:356-368.
10. Frebourg T, Kassel J, Lam KT, et al. Germ-line mutations of the p53 tumor suppressor gene in patients with high risk for cancer inactivate the p53 protein. *Proc Natl Acad Sci.* 1992;89:6413-6417.
11. Frebourg T, Barbier N, Kassel J, et al. A Functional Screen for Germ Line *p53* Mutations Based on Transcriptional Activation. *Cancer Research*. 1992;52:6976-6978.
12. Malcikova J, Tichy B, Damborsky J, et al. Analysis of the DNA-binding activity of p53 mutants using funcational protein microarrays and its relationship to transcriptional activation. *Biol Chem*. 2010;391:197-205.
13. Boutell JM, Hart DJ, Godber BLJ, et al. Functional protein microarrays for parallel characterization of p53 mutants. *Proteomics*. 2004;4:1950-1958.
14. Spurdle AB, Healey S, Devereau A, et al. ENIGMA--evidence-based network for the interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. *Hum Mutat.* 2012;33(1):2-7.
15. Thompson BA, Spurdle AB, Plazzer JP, et al. Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants in the InSiGHT locus-specific database. *Nat Genet.* 2014;46(2):107-115.